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(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH];  
124 Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors: FRIEBE, Walter-Gunar; Sophienstrasse 8,  
68165 Mannheim (DE). MASJOST, Birgit; Paehlstrasse  
12, 81377 Muenchen (DE). SCHUMACHER, Ralf;  
Eichthalstrasse 21, 82377 Penzberg (DE).

(74) Agent: SCHREINER, Siegfried; Roche Diagnostics  
GmbH, Patent Department (TR-E), P.O. Box 11 52, 82372  
Penzberg (DE).

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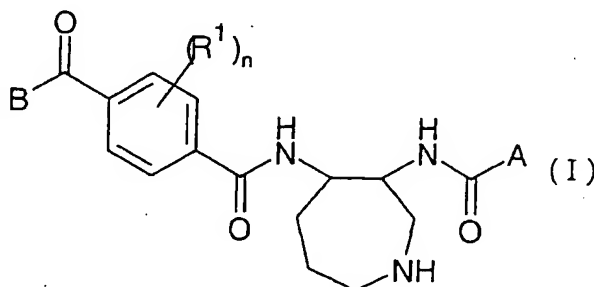
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(54) Title: NOVEL AZEPANE DERIVATIVES



(57) Abstract: This invention provides novel azepane derivatives or pharmaceutically acceptable salts thereof, according to the general formula (I) wherein the remaining symbols have the significance given in the specification, as well as processes for their manufacture. The compounds according to this invention possess anti-cell proliferation activity and show an increased plasma-stability.

### Novel azepane derivatives

5 The invention relates to novel azepane derivatives, or pharmaceutically acceptable salts thereof, which possess anti-cell-proliferation activity such as anti-cancer activity and are accordingly useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said azepane derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

#### 10 Background of the Invention

Cell signaling pathways regulate cell growth, proliferation, and apoptosis. Kinases transduct signals for cell growth or apoptosis by phosphorylation of their substrates which are mostly downstream kinases involved in cell signaling processes themselves. The activity of kinases is regulated by phosphorylation and dephosphorylation effecting conformational changes in the kinases. Overexpression or constitutive activation of kinases involved in anti-apoptotic or proliferation signaling pathways are one typical feature of tumor cells (Cross, T.G., et al., Exp. Cell Res. 256 (2000) 34-41).

20 The family of AKT proteins are located downstream in the PI-3 kinase pathway and phosphorylate a burgeoning list of substrates involved in several pathways for cell survival and inhibition of apoptosis as has been shown recently (Kandel, E.S., and Hay, N., Exp. Cell Res. 253 (1999) 210-229; Blume-Jensen, P., and Hunter, T., Nature 411 (2001) 355-365; Datta, S.R., et al., Genes Dev. 13 (1999) 2905-2927).  
25 Constitutive activation of AKT1 is frequently found in human prostate, breast, and ovarian carcinomas. It is due to a complete loss of lipid phosphatase PTEN gene, a negative regulator of the PI-3 kinase pathway (Nesterov, A., et al., J. Biol. Chem. 276 (2001) 10767-10774). These data indicate that AKT1 kinase is a central player in tumorigenesis and a potential target for cancer intervention. Inhibitors of AKT1  
30 kinase are promising reagents for cancer therapy as effective sensitizers or inducers of apoptosis (Beresford, S.A., et al., J. Interferon Cytokine Res. 21 (2001) 313-322).

AKT1 belongs to the family of protein kinases. It exhibits a sequence homology to PKC and PKA. Several structural classes of PKC and PKA inhibitors are known.

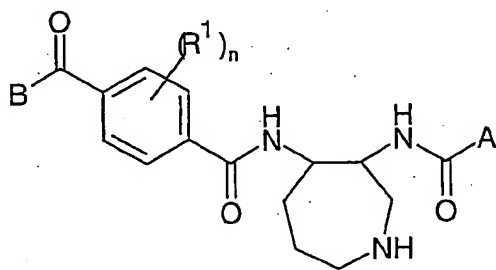
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specifically, WO 94/20062 (by Sphinx Pharmaceuticals Corporation, "Balanol"), WO 95/30640 (by Eli Lilly and company, "Substituted fused and bridged bicyclic compounds as therapeutic agents"), WO 97/02249 (by F. Hoffmann-La Roche, "Novel azepanes and their ring homologues for therapy and prophylaxis of protein kinase mediated diseases"), and EP 0 663 393-A1 (by F. Hoffmann-La Roche, "Neue 3-Amino/Hydroxy-4-[4-Benzoyl-Phenyl Carbonylamino/oxy]-Azepane und Homologe als Protein Kinase Hemmer") report balanol derivatives with PKC inhibitory activity. Bisindolylmaleimides are reported as PKC inhibitors in EP 0 657 458-A1 (by Eli Lilly, "Protein kinase C inhibitors"), EP 1 020 471-A1 (by Kyowa Hakko Kogyo Co., "Process for producing UCN-01"), and EP 0 296 110-A2 (by Ciba-Geigy AG, "An Methylamino-Stickstoff substituierte Derivate von Staurosporin"). No AKT1 small molecule inhibitors are reported in the literature.

It has now been found that certain novel azepane derivatives are potent inhibitors of AKT1 in vitro and in various tumor cell lines, possess anti-cell-proliferation properties, induce apoptosis and are plasma stable which makes them more potent than those in the aforementioned references.

### Description of the Invention

According to the invention there is provided a novel azepane derivative of the formula I



(I)

wherein

25

A denotes

- a carbocyclic group

- 3 -

- a heterocyclic group

n is 0-4

5 each R<sup>1</sup> is the same or different residue, independently selected from the group consisting of a halogen atom, a (1-4C)alkyl-, or a (1-4C)alkoxy- group,

B denotes

- 10 • a phenyl ring which may be unsubstituted or substituted by 1,2, or 3 substituents independently selected from a halogen atom, an (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, nitro, amino, amino(1-4C)alkyl, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-4C)alkanoylamino, (1-4C)alkylthio, (1-4C)alkoxycarbonyl, a (1-3C)alkylenedioxy, an acyl, a carbocyclic or a heterocyclic group, and which may be annulated by a carbocyclic group or by a  
15 heterocyclic group, or
- a heterocyclic group, its stereoisomers, enantiomers and racemates, and pharmaceutically acceptable salts thereof.

A carbocyclic group may be

- 20 • a non-aromatic, preferably mono- or bicyclic ring system with 3-7 carbon atoms, for example cyclopentane, cyclohexane, cyclohexene or cyclopropane, which may be unsubstituted or substituted by 1, 2, or 3 substituents independently selected from a halogen atom, an (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, aryl, hetaryl, arylalkyl, arylalkyloxy, aryloxy, (1-3C)alkylenedioxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-4C)alkanoylamino or an acyl group, and which may be annulated by an aryl or  
25 hetaryl group, to form e.g. an indane or a tetraline,
- or it may be an aryl group.

30 An aryl group is a carbocyclic, preferably mono- or bicyclic, conjugated ring system, for example phenyl, naphthyl, preferably phenyl, which may be unsubstituted or substituted by 1, 2, or 3 substituents independently selected from a halogen atom, an (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, arylalkyloxy, aryloxy, (1-3C)alkylenedioxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-4C)alkanoylamino, or an acyl group.  
35

A heterocyclic group may be

- a non-aromatic, preferably mono- or bicyclic ring system with 3-7 members and one or two hetero atoms independently chosen from nitrogen, oxygen, and sulfur, for example piperidino, morpholino, pyrrolidino, piperazino, which may be unsubstituted or substituted by 1, 2, or 3 substituents independently selected from a halogen atom, an (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, aryl, hetaryl, arylalkyl, arylalkyloxy, aryloxy, (1-3C)alkylenedioxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-4C)alkanoylamino, or an acyl group, and which may be annulated by an aryl or hetaryl group, to form e.g. a tetrahydroquinoline, tetrahydroisoquinoline or a dihydroindole,
- or it may be a hetaryl group.

A hetaryl group may be either a 5 or 6 membered cyclic conjugated ring system with one or two hetero atoms independently chosen from nitrogen, oxygen, and sulfur, for example pyridinyl, pyrimidinyl, thiophenyl, furyl or pyrrolyl, or an annulated bicyclic conjugated ring system like indolyl, quinolyl or isoquinolyl, which may be unsubstituted or substituted by 1, 2, or 3 substituents independently selected from a halogen atom, an (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, arylalkyloxy, aryloxy, (1-3C)alkylenedioxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-4C)alkanoylamino, or an acyl group.

A preferred value for a substituent when it is a halogen atom is, for example, fluoro, chloro, bromo and iodo; when it is (1-4C)alkyl is, for example, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert.-butyl; when it is (1-4C)alkoxy is, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy; when it is amino(1-4C)alkyl is, for example, aminomethyl, 1- or 2-aminoethyl or 1-, 2- or 3-aminopropyl; when it is (1-4C)alkylamino is, for example, methylamino, ethylamino or propylamino; when it is di-[(1-4C)alkyl]amino is, for example, dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino or dipropylamino; when it is (1-4C)alkanoylamino is, for example, formylamido, acetamido, propionamido or butyramido; when it is (1-3C)alkylenedioxy is, for example, methylenedioxy, ethylenedioxy or propylenedioxy; and when it is acyl is, for example, formyl, acetyl, propionyl, benzoyl, or phenylacetyl.

Enantiomers, diastereoisomers, racemates and mixtures thereof and pharmaceutically acceptable salts of azepane derivatives of the formula I are also part of the invention.

- 5 -

“Pharmaceutically acceptable salt” refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of formula I and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. The chemical modification of a pharmaceutical compound (i.e., a drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. See, e.g., H. Ansel et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 196 and 1456-1457.

A preferred embodiment of the invention are the compounds of formula (I), wherein

- A is a carbocyclic or heterocyclic group;
- B is a phenyl ring which may be unsubstituted or substituted by 1, 2 or 3 substituents independently selected from a halogen atom, an (1-4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, nitro, amino, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-4C)alkanoylamino, (1-4C)alkylthio, (1-4C)alkoxycarbonyl, a (1-3C)alkylenedioxy, an acyl, a carbocyclic or a heterocyclic group, and which may be annulated by a carbocyclic group or by a heterocyclic group, or a heterocyclic group,

its stereoisomers, enantiomers and racemates, and salts thereof;

- (R<sup>1</sup>)<sub>n</sub> is the same or different halogen atom, a (1-4C)alkyl-, or a (1-4C)alkoxy- group, and n = 0-4.

Another preferred embodiment of the invention are the compounds of formula ( I ), wherein

A is Pyridine, 2-Aminopyridine or Pyrimidine;

B is a substituent, chosen from:

- 5 2-Fluoro-6-hydroxy-3-methoxy-phenyl, 2-Fluoro-6-hydroxy-3-methyl-phenyl, 6-Hydroxy-3-methylsulfanyl-phenyl, 6-Hydroxy-2,3-dihydrobenzo[1,4]dioxine-5-yl, 6-Hydroxy-2,3-dimethoxy-phenyl, 2-Hydroxy-5-methoxy-phenyl, 2-Hydroxy-5-methyl-phenyl, 5-Hydroxy-2-methylpyridine-4-yl, 3-Fluoro-5-hydroxy-2-methyl-pyridine-4-yl, 8-Fluoro-6-hydroxy-quinoline-7-yl, 8-Fluoro-6-hydroxy-2-methyl-quinoline-7-yl, 2-tert-Butyl-8-fluoro-6-hydroxy-quinoline-7-yl, 6-Hydroxy-quinoline-5-yl, 3-Dimethylamino-2-fluoro-6-hydroxy-phenyl, 5-Dimethylamino-2-hydroxy-phenyl, 2-Hydroxy-5-piperidin-1-yl-phenyl, 2-Fluoro-6-hydroxy-3-piperidin-1-yl-phenyl, 3-(3,3-Dimethyl-piperidin-2-yl)-2-fluoro-6-hydroxy-phenyl, 3-(3,3-Dimethyl-piperidin-2-yl)-6-hydroxy-phenyl;
- 10  
15

and  $n = 0$  for  $(R^1)_n$ .

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an azepane derivative of the formula I, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier. The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. In general the above compositions may be prepared in a manner using conventional excipients. The azepane derivative will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-100 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the

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30

illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided an azepane derivative of the formula I as defined hereinbefore for use in a method of treatment  
5 of the human or animal body by therapy. It has now been found that the compounds of the present invention possess anti-cell-proliferation properties which are believed to arise from their AKT1 inhibitory activity. Accordingly the compounds of the present invention provide a method for treating the proliferation  
10 of malignant cells. Accordingly the compounds of the present invention are expected to be useful in the treatment of cancer by providing an anti-proliferative effect, particularly in the treatment of cancers of the breast, lung, colon, rectum, stomach, prostate, bladder, pancreas and ovary. It is in addition expected that a derivative of the present invention will possess activity against a range of leukemias, lymphoid malignancies and solid tumors such as carcinomas and sarcomas in  
15 tissues such as the liver, kidney, prostate and pancreas.

Thus according to this aspect of the invention there is provided the use of an azepane derivative of the formula I, or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as a human being.

20 According to a further feature of this aspect of the invention there is provided a method for producing an anti-cell-proliferation effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of an azepane derivative as defined hereinbefore.

The anti-cell-proliferation treatment defined hereinbefore may be applied as a sole  
25 therapy or may involve, in addition to the azepane derivative of the invention, one or more other anti-tumor substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; inhibitors of microtubule assembly, like paclitaxel or other taxanes; antimetabolites, for example 5-fluorouracil,  
30 capecitabine, cytosine arabinoside and hydroxyurea, or, for example, intercalating antibiotics, for example adriamycin and bleomycin; immunostimulants, for example trastuzumab; DNA synthesis inhibitors, e.g. gemcitabine; enzymes, for example asparaginase; topoisomerase inhibitors, for example etoposide; biological



response modifiers, for example interferon; and anti-hormones, for example antiestrogens such as tamoxifen or, for example antiandrogens such as (4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propion-anilide, or other therapeutic agents and principles as described in, for example, 5 Cancer: Principles & Practice of Oncology, Vincent T. DeVita, Jr., Samuel Hellmann, Steven A. Rosenberg; 5th ed., Lippincott-Raven Publishers, 1997. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising an azepane 10 derivative of the formula I as defined hereinbefore and an additional anti-tumor substance as defined hereinbefore for the conjoint treatment of cancer.

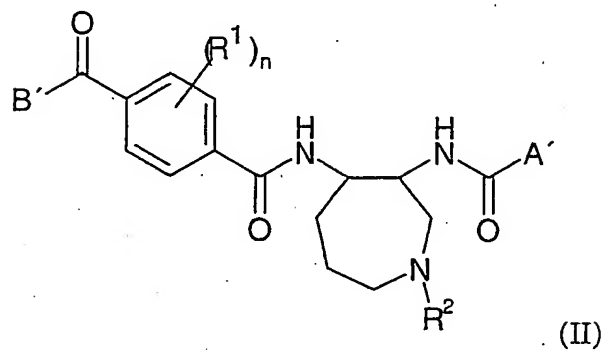
Another object of the present invention are pharmaceutical compositions containing a pharmacologically effective amount of one or more compounds of formula I in admixture with pharmaceutically acceptable excipients and/or 15 diluents.

Examples for physiologically acceptable salts of compounds of formula I are salts with physiologically acceptable acids. These salts can be, among others, hydrochloride, sulfate, mesylate, succinate, tartrate, acetate, and phosphate.

#### Preparation of the Compounds of the Invention

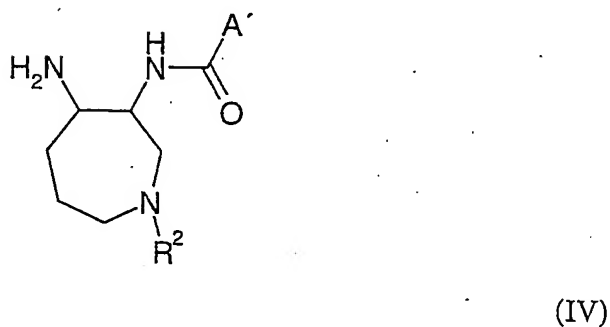
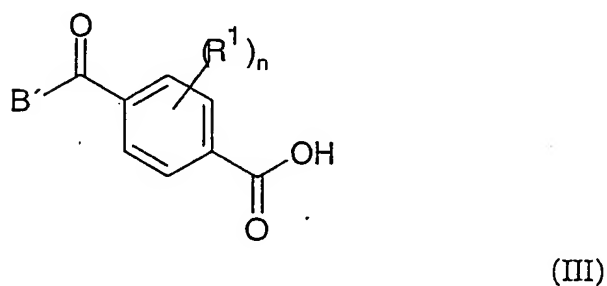
20 An azepane derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare an azepane derivative of the formula I, or a pharmaceutically-acceptable salt thereof, are 25 provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated, A, B and R<sup>1</sup> have any of the meanings defined hereinbefore and R<sup>2</sup> is a suitable protecting group, preferably t-butoxycarbonyl or methoxymethyl. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting 30 materials is described within the accompanying non-limiting examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

The preferred method for the production of compounds of formula I involves the reaction of compounds of formula II



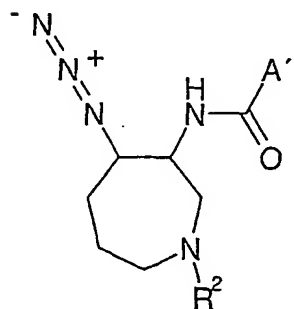
- 5 wherein R<sup>1</sup> and R<sup>2</sup> have the meaning defined hereinbefore and A' and B' represent A and B as defined hereinbefore, or a suitably protected derivative thereof, with a deprotecting agent, e.g. HCl in dioxane at room temperature. Suitable protecting groups are e.g. t-butoxycarbonyl or methoxymethyl.

10 Compounds of formula II are prepared from compounds of formula III and IV wherein A', B', R<sup>1</sup> and R<sup>2</sup> have the meaning defined hereinbefore.



This reaction typically involves a two-step one-pot procedure. In the first step, the  
 carboxylate of the formula III becomes activated. This reaction is carried out in an  
 inert solvent or diluent, for example, in dichloromethane, dioxane, or  
 5 tetrahydrofuran, in the presence of an activating agent. A suitable reactive  
 derivative of an acid is, for example, the product of the reaction of the acid and a  
 carbodiimide such as dicyclohexylcarbodiimide, or the product of the reaction of  
 the acid and bis-(2-oxo-3-oxazolidinyl)-phosphorylchloride; or the product of the  
 10 reaction of the acid and carbonyldiimidazole; or the product of the reaction of the  
 acid and N-hydroxysuccinimide; an acyl halide, for example an acyl chloride  
 formed by the reaction of the acid and an inorganic acid chloride, for example  
 thionyl chloride; a mixed anhydride, for example an anhydride formed by the  
 reaction of the acid and a chloroformate such as isobutyl chloroformate; an active  
 15 ester, for example an ester formed by the reaction of the acid and a phenol such as  
 pentafluorophenol; an active ester formed by the reaction of the acid and N-  
 hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of  
 the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for  
 example a cyanide formed by the reaction of an acid and a cyanide such as  
 20 diethylphosphoryl cyanide. The activation reaction is carried out between -30°C  
 and 60°C, conveniently at or below 0°C. In the second step, the amine of the  
 formula IV is added to the solution, at the temperature used for the activation, and  
 the temperature is slowly adjusted to ambient temperature. An appropriate  
 scavenger base like e.g. dimethylaminopyridine, triethylamine, or  
 diisopropylethylamine may be added to the reaction mixture. These methods are  
 25 well known to those skilled in the art. In principle, all methods for the synthesis of  
 amides as used in peptide chemistry as described in e.g. "Methoden der organischen  
 Chemie (Houben-Weyl)" Band XV/1 and XV/2 are also applicable.

Compounds of formula IV may be prepared from compounds of formula V,

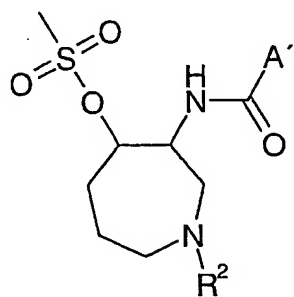


(V)

- 11 -

wherein A' and R<sup>2</sup> have the meaning defined hereinbefore, by reaction of V with hydrogen and e.g. 10% Pd/C in THF and ethanol or Raney-Nickel in methanol at room temperature at 1 bar.

Compounds of formula V may be prepared from compounds of formula VI,

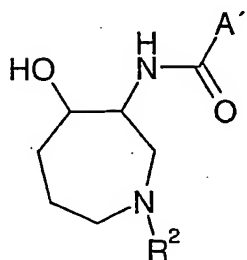


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(VI)

wherein A' and R<sup>2</sup> have the meaning defined hereinbefore, by reaction of VI with e.g. sodium azide in DMF at 60-90°C.

Compounds of the formula VI may be prepared from compounds of the formula VII,



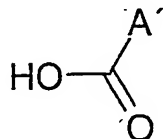
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(VII)

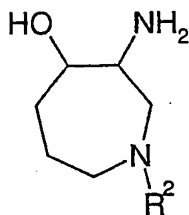
wherein A' and R<sup>2</sup> have the meaning defined hereinbefore, by reaction of VII with methylsulfonyl chloride e.g. in pyridine at 0 °C.

- 12 -

Compounds of the formula VII are prepared from compounds of the formula VIII and compound IX, wherein A' and R<sup>2</sup> have the meaning defined hereinbefore,



(VIII)



(IX)

5

This reaction typically involves a two-step one-pot procedure. In the first step, the carboxylate of the compound of formula VIII becomes activated by any of the methods as described for formula III. In the second step, the amine of formula IX is added to the solution in the same way as described for the amine IV.

10 Compounds of formula VIII are commercially available or synthesized by literature-known procedures and are well known to those skilled in the art.

The synthesis of compound IX is described in EP 0 802 190 A1.

Compounds of formula III are prepared as described in EP 0 663 393 A1 and WO 97/702249.

15 The invention will now be illustrated in the following non-limiting examples in which, unless otherwise stated:

- (i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

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- 13 -

- (ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;
- (iii) column chromatography (by the flash procedure) and high pressure liquid chromatography (HPLC) were performed on Merck Kieselgel silica or Merck Lichroprep RP-18 reversed-phase silica obtained from E. Merck, Darmstadt, Germany;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) melting points were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Kofler hot plate apparatus.
- (vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques (Micromass Platform II machine using APCI or Micromass Platform ZMD using electrospray);
- (vii) intermediates were not generally fully characterized and purity was assessed by thin layer chromatography;
- (viii) the following abbreviations have been used:
- DMF, N,N-dimethylformamide;  
DMSO, dimethylsulfoxide;  
THF, tetrahydrofuran;  
MeOH, methanol;  
HCl, hydrochloric acid;  
NaH, sodium hydride  
CH<sub>2</sub>Cl<sub>2</sub>, dichloromethane;  
H<sub>2</sub>SO<sub>4</sub>, sulfuric acid  
sat., saturated  
sol., solution  
rt, room temperature  
eq, equivalent  
mp, melting point

The following examples and references are provided to aid the understanding of the present invention, the true scope of which is set forth in the appended claims. It is understood that modifications can be made in the procedures set forth without departing from the spirit of the invention.

#### Example 1a

*N*-{(3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-methoxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride (1a)

0.05 g of 1b are dissolved in 2 mL of a solution of hydrochloric acid in dioxane (4M) at rt and stirred for 24 h. The solvents are evaporated *in vacuo* and the residue is redissolved in methanol and evaporated to dryness for three times yielding 0.038 g (82 %) of 1a as light yellow crystals. MS (ESI): *m/z* (%): 507 (*MH*<sup>+</sup>), 505 ([*M-H*]<sup>+</sup>). Mp. 200-222°C

#### Example 1b

(3*R*,4*R*)-4-[4-(2-Fluoro-6-methoxymethoxy-3-methoxy-benzoyl)-benzoylamino]-3-[(pyridine-4-carbonyl)-amino]-azepane-1-carboxylic acid *tert*-butyl ester (1b)

0.167 g of 1c are dissolved in 5 mL CH<sub>2</sub>Cl<sub>2</sub> at rt. 0.167 g of 4-(2-Fluoro-3-methoxy-6-methoxymethoxy-benzoyl)-benzoic acid (1d), 0.031 g 4-dimethylaminopyridine, and 0.113 g DCC are added. The reaction mixture is stirred for 5 h at rt. The precipitate is filtered off and washed with CH<sub>2</sub>Cl<sub>2</sub>. The residue is evaporated *in vacuo* to give 0.46 g of crude product. Column chromatography (SiO<sub>2</sub>, pentane/ethyl acetate 1:10) afforded 0.248 g (76 %) of 1b as white crystals. M. p. 106 °C; MS (ESI): *m/z* (%): 651 (*MH*<sup>+</sup>), 649 ([*M-H*]<sup>+</sup>).

#### Example 1c

(3*R*,4*R*)-4-Amino-3-[(pyridine-4-carbonyl)-amino]-azepane-1-carboxylic acid *tert*-butyl ester (1c)

5.5 g of 1e are dissolved in 135 mL THF and 15 mL ethanol and 1 g Pd/C (10%) is added. The reaction mixture is hydrogenated at 1 bar for 8 h. After filtration, the residue is evaporated *in vacuo* to give 4.6 g (90%) of 1c as a light brown powder. MS (ESI): *m/z* (%): 335 (*MH*<sup>+</sup>), 333 ([*M-H*]<sup>+</sup>).

The synthesis of 1d (4-(2-Fluoro-3-methoxy-6-methoxymethoxy-benzoyl)-benzoic acid) is described in EP 0 663 393 A1.

Example 1e

5 (3R,4R)-4-Azido-3-[(pyridine-4-carbonyl)-amino]-azepane-1-carboxylic acid *tert*-butyl ester (1e)

6.4 g of 1f are dissolved in 150 mL DMF and 5.1 g sodium azide are added. The reaction mixture is stirred for 2 h at 90 °C and then for 24 h at rt. The solvents are evaporated *in vacuo* and the residue is redissolved in 200 mL ethyl acetate. The organic phase is extracted two times with 200 mL water and once with a saturated solution of NaCl. The organic phase is evaporated *in vacuo* to give 5.6 g of crude product. Column chromatography (SiO<sub>2</sub>, hexane/ethyl acetate 3:7) affords 5.4 g (97 %) of 1e as light brown solid. MS (ESI): *m/z* (%): 361 (MH<sup>+</sup>), 359 ([M-H]<sup>+</sup>).

Example 1f

15 (3R,4S)-4-Methanesulfonyloxy-3-[(pyridine-4-carbonyl)-amino]-azepane-1-carboxylic acid *tert*-butyl ester (1f)

6.6 g of 1g are dissolved in 100 mL pyridine and 6.76 g methanesulfonyl chloride are added at 0 °C. The reaction mixture is stirred for 24 h. The solvent is evaporated *in vacuo* and the residue is redissolved in 100 mL ethyl acetate and extracted three times with water and once with a saturated solution of NaCl. The organic phase is evaporated *in vacuo*. Column chromatography (SiO<sub>2</sub>, ethyl acetate/methanol 99:1) gives 6.4 g (79 %) of 1f as a white foam. MS (ESI): *m/z* (%): 414 (MH<sup>+</sup>), 412 ([M-H]<sup>+</sup>).

Example 1g

25 (3R,4S)-4-Hydroxy-3-[(pyridine-4-carbonyl)-amino]-azepane-1-carboxylic acid *tert*-butyl ester (1g)

36.85 g of (3R,4S)-3-Amino-4-hydroxy-azepane-1-carboxylic acid *tert*-butyl ester, 19.70 g 4-pyridinecarboxylic acid, and 9.76 g dimethylaminopyridine are dissolved in 500 mL CH<sub>2</sub>Cl<sub>2</sub> and cooled to 5 °C. 33.01 g DCC are dissolved in 250 mL CH<sub>2</sub>Cl<sub>2</sub> and added to the above mixture within 2 h. The reaction mixture is stirred for 48 h at rt. 200 mL water are added and the mixture is stirred for 2 h at rt. The precipitate is filtered off and the organic phase is extracted two times with 500 mL



water. The organic solvent is evaporated *in vacuo*. The crude product is then submitted to column chromatography (SiO<sub>2</sub>, ethyl acetate/methanol 99:1) to give 46.2 g (86 %) of 1g as a white solid. MS (ESI): *m/z* (%): 334 (MH<sup>+</sup>), 336 ([M-H]<sup>+</sup>).

### Example 2

5

In an analogous manner as described in Example 1, the following compounds are obtained and characterized by melting points..

1. *N*-{(3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-methyl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 181-184 °C
- 10 2. *N*-{(3*R*,4*R*)-4-[4-(6-Hydroxy-3-methylsulfanyl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 183-185 °C
3. *N*-{(3*R*,4*R*)-4-[4-(6-Hydroxy-2,3-dihydro-benzo[1,4]dioxine-5-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 230-240°C
- 15 4. *N*-{(3*R*,4*R*)-4-[4-(6-Hydroxy-2,3-dimethoxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 185-193 °C
5. *N*-{(3*R*,4*R*)-4-[4-(2-Hydroxy-5-methoxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 230-240 °C
- 20 6. *N*-{(3*R*,4*R*)-4-[4-(2-Hydroxy-5-methyl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 215-219 °C
7. *N*-{(3*R*,4*R*)-4-[4-(5-Hydroxy-2-methyl-pyridine-4-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 203-208°C
- 25 8. *N*-{(3*R*,4*R*)-4-[4-(3-Fluoro-5-hydroxy-2-methyl-pyridine-4-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.

9. *N*-{(3*R*,4*R*)-4-[4-(8-Fluoro-6-hydroxy-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 247-251°C
- 5 10. *N*-{(3*R*,4*R*)-4-[4-(8-Fluoro-6-hydroxy-2-methyl-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 255-260°C
11. *N*-{(3*R*,4*R*)-4-[4-(2-*tert*-Butyl-8-fluoro-6-hydroxy-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 215 °C
- 10 12. *N*-{(3*R*,4*R*)-4-[4-(6-Hydroxy-quinoline-5-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 215-220 °C
13. *N*-{(3*R*,4*R*)-4-[4-(3-Dimethylamino-2-fluoro-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
14. *N*-{(3*R*,4*R*)-4-[4-(5-Dimethylamino-2-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 230-245 °C
- 15 15. *N*-{(3*R*,4*R*)-4-[4-(2-Hydroxy-5-piperidin-1-yl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 218-224 °C
16. *N*-{(3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-piperidin-1-yl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 20 17. *N*-{(3*R*,4*R*)-4-[4-[3-(3,3-Dimethyl-piperidin-2-yl)-2-fluoro-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 265°C
18. *N*-{(3*R*,4*R*)-4-[4-[3-(3,3-Dimethyl-piperidin-2-yl)-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 25 19. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(2-fluoro-6-hydroxy-3-methoxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 223-241°C

- 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-methyl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
21. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(6-hydroxy-3-methylsulfanyl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 5 22. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(6-Hydroxy-2,3-dihydro-benzo[1,4]dioxine-5-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
23. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(6-Hydroxy-2,3-dimethoxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
24. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(2-Hydroxy-5-methoxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 10 25. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(2-Hydroxy-5-methyl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
26. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(5-Hydroxy-2-methyl-pyridine-4-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 15 27. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(3-Fluoro-5-hydroxy-2-methyl-pyridine-4-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
28. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(8-Fluoro-6-hydroxy-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
29. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(8-Fluoro-6-hydroxy-2-methyl-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 20 30. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(2-*tert*-Butyl-8-fluoro-6-hydroxy-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
31. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(6-Hydroxy-quinoline-5-carbonyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.

- 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(3-Dimethylamino-2-fluoro-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
33. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(5-Dimethylamino-2-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 5 34. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(2-Hydroxy-5-piperidin-1-yl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
35. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-piperidin-1-yl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 10 36. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-[3-(3,3-Dimethyl-piperidin-2-yl)-2-fluoro-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
37. 2-Amino-*N*-{(3*R*,4*R*)-4-[4-[3-(3,3-Dimethyl-piperidin-2-yl)-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
- 15 38. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(2-fluoro-6-hydroxy-3-methoxy-benzoyl)-benzoylamino]-azepan-3-yl}-amide hydrochloride. Mp. 256-265 °C
39. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-methyl-benzoyl)-benzoylamino]-azepan-3-yl}-amide hydrochloride.
- 20 40. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(6-hydroxy-3-methylsulfanyl-benzoyl)-benzoylamino]-azepan-3-yl}-amide hydrochloride.
41. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(6-Hydroxy-2,3-dihydro-benzo[1,4]dioxine-5-carbonyl)-benzoylamino]-azepan-3-yl}-amide hydrochloride.
- 25 42. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(6-Hydroxy-2,3-dimethoxy-benzoyl)-benzoylamino]-azepan-3-yl}-amide hydrochloride.

- Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(2-Hydroxy-5-methoxy-benzoyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
44. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(2-Hydroxy-5-methyl-benzoyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
- 5 45. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(5-Hydroxy-2-methyl-pyridine-4-carbonyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
46. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(3-Fluoro-5-hydroxy-2-methyl-pyridine-4-carbonyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
- 10 47. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(8-Fluoro-6-hydroxy-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
48. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(8-Fluoro-6-hydroxy-2-methyl-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
- 15 49. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(2-*tert*-Butyl-8-fluoro-6-hydroxy-quinoline-7-carbonyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
50. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(6-Hydroxy-quinoline-5-carbonyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
- 20 51. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(3-Dimethylamino-2-fluoro-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
52. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(5-Dimethylamino-2-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
- 25 53. Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(2-Hydroxy-5-piperidin-1-yl-benzoyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.

- Pyrimidine-4-carboxylic acid {(3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-piperidin-1-yl-benzoyl)-benzoylamino]-azepan-3-yl}- amide hydrochloride.
55. Pyrimidine-4-carboxylic acid ((3*R*,4*R*)-4-[4-[3-(3,3-Dimethyl-piperidin-2-yl)-2-fluoro-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl)- amide hydrochloride.
56. Pyrimidine-4-carboxylic acid ((3*R*,4*R*)-4-[4-[3-(3,3-Dimethyl-piperidin-2-yl)-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl)- amide hydrochloride.
57. *N*-{(3*R*,4*R*)-4-[4-(3-Methyl-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 190-196 °C
58. *N*-{(3*R*,4*R*)-4-[4-(2,5-Dihydroxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 108-114°C
59. *N*-{(3*R*,4*R*)-4-[4-(2-Hydroxy-5-isopropoxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 243-249 °C
60. *N*-{(3*R*,4*R*)-4-[4-(3-Aminomethyl-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride. Mp. 215-218 °C
61. *N*-{(3*R*,4*R*)-4-[4-(3-<1-Amino-cyclopropyl>-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl}-isonicotinamide hydrochloride.
62. *N*-((3*R*,4*R*)-4-[4-[2-Hydroxy-5-(piperidin-2-yl)-benzoyl]-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride. Mp. 195-210 °C
63. *N*-((3*R*,4*R*)-4-[4-[3-(3,3-Dimethyl-piperidin-1-yl)-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride. Mp. 194-198°C
64. *N*-((3*R*,4*R*)-4-[4-[3-(3,3-Dimethyl-piperidin-1-yl)-2-fluoro-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride.

- N*-((3*R*,4*R*)-4-[4-[3-(4,4-Dimethyl-piperidin-1-yl)-6-hydroxy-benzoyl]-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride. Mp. 229-234°C
- 5      66.    *N*-((3*R*,4*R*)-4-[4-(2-Hydroxy-5-isopropylamino-benzoyl)-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride. Mp. 227-230 °C
67.    *N*-((3*R*,4*R*)-4-[4-(2-Hydroxy-5-(2-methyl-propylamino)-benzoyl)-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride. Mp. 223-226°C
- 10      68.    *N*-((3*R*,4*R*)-4-[4-(3-(2,2-Dimethyl-propylamino)-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride. Mp. 243-246°C
69.    *N*-((3*R*,4*R*)-4-[4-(2,5-Dimethoxy-6-fluoro-benzoyl)-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride
- 15      70.    *N*-((3*R*,4*R*)-4-[4-(3-(3-Azabicyclo[3.2.1]oct-3-yl)-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl)-isonicotinamide hydrochloride.
71.    4-Hydroxybenzoic acid ((3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-methoxy-benzoyl)-benzoylamino]-azepan-3-yl)- amide hydrochloride. Mp. 190-196°C
- 20      72.    4-Hydroxybenzoic acid ((3*R*,4*R*)-4-[4-(3-Dimethylamino-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl)- amide hydrochloride. Mp. 203-206°C
73.    3,5-Dimethyl-4-hydroxybenzoic acid ((3*R*,4*R*)-4-[4-(2-Fluoro-6-hydroxy-3-methoxy-benzoyl)-benzoylamino]-azepan-3-yl)- amide hydrochloride. Mp. 180-183 °C
- 25      74.    3,5-Dimethyl-4-hydroxybenzoic acid ((3*R*,4*R*)-4-[4-(3-Dimethylamino-6-hydroxy-benzoyl)-benzoylamino]-azepan-3-yl)- amide hydrochloride. Mp. 217-219 °C

### Example 3

In order to study AKT inhibitory activity of the compounds according to the invention, an ELISA-based assay has been developed for the serine/threonine kinase, AKT. The assay design utilizes a N-terminally biotinylated substrate peptide. When this substrate is phosphorylated by the AKT kinase, the product is recognized by a substrate/sequence-specific antibody known to bind to particular phosphorylated serine residues. For this assay a Biotin-SGRARTSSFAEPG peptide and anti-phospho-GSK-3 $\alpha$  Ser21 antibody (rabbit) from Cell Signaling Technology/New England Biolabs have been used.

The enzymatic reactions were carried out with AKT expressed in Sf9 cells (100 ng/reaction), substrate peptide (300nM) and ATP (5 $\mu$ M) in the absence or presence of different concentrations of compounds dissolved in DMSO. The final concentration of DMSO was 1%. The mixtures were reacted for 30' at room temperature in assay buffer containing 50 mM Tris-HCl, 10 mM MgCl<sub>2</sub>, 1.0 mM DTT, 2 mM Na<sub>3</sub>VO<sub>4</sub>, pH 7.5, in a final volume of 40 $\mu$ l. The reaction was stopped with addition of 10 $\mu$ l 0,12 M EDTA/0,12 M EGTA. The reaction mixture was transferred to a SA-coated micro-titer-plate. After 1 h incubation the plate was washed with PBS using a 384-well Embla plate washer. Anti-phospho-GSK-3 $\alpha$  Ser21 antibody was added. After 1 h incubation the plate was washed with PBS and bound antibody was detected by addition of polyclonal<Rabbit>S-IgG-POD-conjugate from Roche Diagnostics GmbH. After 1 h incubation the plate was washed with PBS. Amount of phosphorylated peptide was measured by an enzyme-catalyzed color reaction (ABTS conversion) and photometrical measurement at 405 nm.

To determine IC<sub>50</sub> values the compounds were tested in the concentration range from 250nM to 10pM. Calculation of IC<sub>50</sub> values were performed with ActivityBase. The compounds according to the invention gave IC<sub>50</sub> values in the range of 3 to 116 nM, e.g. for the following but non limiting Examples 1a, 2-1, 2-2, 2-4, 2-5, 2-6 values of 3, 7, 11, 116, 15 and 16 nM were determined respectively.

### Example 4

Additionally to Example 3 the activity of compounds according to the invention was studied on a cellular AKT activity assay as follows:



- 24 -

Prostate cancer cell line LNCaP was passaged in RPMI 1640 with 10% fetal calf serum, 50 units/ml penicillin, and 50 units/ml streptomycin. LNCaP cells are characterized by a constitutive activation of AKT. Constitutive active AKT phosphorylates glycogen synthase kinase-3 (GSK-3) at Ser21/Ser9 in LNCaP cells.

5 To measure the effect of compounds on the activity of AKT in living cells LNCaP cells were treated with various concentrations of inhibitors (6 $\mu$ M to 187nM). After 1 h the cells were harvested in lysis solution containing 50 mM HEPES (pH 7.0), 150 mM NaCl, 1.5 mM MgCl<sub>2</sub>, 1 mM EGTA, 100 mM NaF, 10 mM sodium PPi, 10% glycerol, 1% Triton X-100, 1 mM Na<sub>3</sub>VO<sub>4</sub>, 10mM pepstatin, 10 mg/ml

10 aprotinin, 5 mM iodoacetic acid, and 2 mg/ml leupeptin. The proteins from whole cell extracts were electrophoresed on 7.5% SDS/PAGE gels. Afterwards proteins were transferred onto Nitrocellulose filter and immunoblotting using the enhanced chemiluminescence (ECL) detection system (Amersham Pharmacia) was performed. The level of GSK-3-Ser21/Ser9 phosphorylation was thereby

15 determined using polyclonal anti-P-GSK-3-Ser-21/9 antibody (rabbit; New England Biolabs). Here, for the above-mentioned, but non limiting Examples 1a, 2-1, 2-2, 2-4, 2-5, 2-6 values of 3, 3, 1.5, >24, 2 and 1  $\mu$ M were found respectively.

#### Example 5

20 In order to prove the increased plasma-stability of the compounds according to this invention, mouse plasma tests have been used as follows:

Samples of mouse plasma containing each a compound according to the invention in a standard concentration ( 10  $\mu$ mol / l ) were prepared. After defined periods of time with respect to the addition of said compounds to the mouse-plasma ( t = 0,

25 0.5, 1, 2, 4 h ), equal portions were isolated from the plasma, separated with HPLC and analyzed by Mass Spectrometry. During all these steps, the temperature was kept constant at 37 °C.

In the following table, the plasma stability of compounds according to the invention is compared to one of the favorite compounds from EP 0 663 393 A1.

- 25 -

Table 1

Reference-Compound from EP 0 663 393 A1	Decrease [ % ]
Example 46	100 ( after 2 h )

Compounds according to the invention	Decrease [ % ] (after 4h)
Example 1a	6,2
Example 2-1	21,9
Example 2-2	26,9

Example 6

5

## Tablet formulation

Item	Ingredients	mg/Tablet	
1	Compound 2-1	25	100
2	Anhydrous Lactose	73	35
3	Croscarmellose	6	8
	Sodium		
4	Povidone K30	5	6
5	Magnesium Stéarate	1	1
	Total Weight	110	150

Compound 2-1 is described in Example 2.

10

## Procedure:

1. Mix Items 1, 2 and 3 in a suitable mixer for 15 minutes.
2. Granulate the powder mix from Step 1 with 20% Povidone K30 Solution (Item 4).
- 15 3. Dry the granulation from Step 2 at 50° C.
4. Pass the granulation from Step 3 through a suitable milling equipment.
5. Add the Item 5 to the milled granulation Step 4 and mix for 3 minutes.
6. Compress the granulation from Step 5 on a suitable press.

Example 7

## Capsule formulation

Item	Ingredients	mg/Capsule	
1	Compound 2-1	50	100
2	Anhydrous Lactose	123	148
3	Corn Starch	35	40
4	Talc	15	10
5	Magnesium Stearate	2	2
	Total Fill Weight	225	300

5

Compound 2-1 is described in Example 2.

## Manufacturing Procedure:

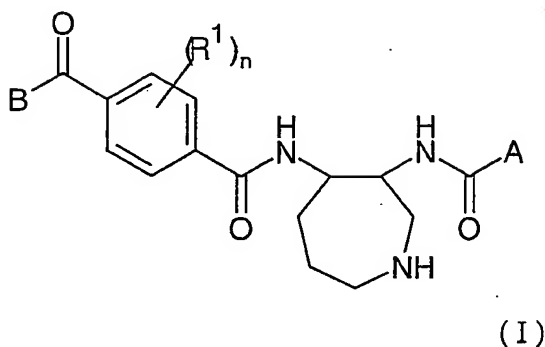
- 10
1. Mix Items 1, 2 and 3 in a suitable mixer for 15 minutes.
  2. Add Items 4 & 5 and mix for 3 minutes.
  3. Fill into a suitable capsule.

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## Patent Claims

1. A compound of formula ( I ) or a salt thereof



wherein

- 5        A    is a carbocyclic or heterocyclic group;  
       B    is a phenyl ring which may be unsubstituted or substituted by 1, 2 or 3  
           substituents independently selected from a halogen atom, an (1-  
           4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, nitro, amino,  
           amino(1-4C)alkyl, (1-4C)alkylamino, di[(1-4C)alkyl]amino, (1-  
 10        4C)alkanoylamino, (1-4C)alkylthio, (1-4C)alkoxycarbonyl, a (1-  
           3C)alkylenedioxy, an acyl, a carbocyclic or a heterocyclic group, and  
           which may be annulated by a carbocyclic group or by a heterocyclic  
           group, or  
           a heterocyclic group,

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its stereoisomers, enantiomers and racemates, and salts thereof;

( R<sup>1</sup> )<sub>n</sub> is the same or different halogen atom, a (1-4C)alkyl-, or a (1-  
 4C)alkoxy- group, and n = 0-4.

2. A compound of formula ( I ) according to claim 1, wherein

20

- A    is a carbocyclic or heterocyclic group;  
 B    is a phenyl ring which may be unsubstituted or substituted by 1, 2 or 3  
       substituents independently selected from a halogen atom, an (1-  
       4C)alkyl, trifluoromethyl, hydroxy, (1-4C)alkoxy, nitro, amino, (1-

4C)alkylamino, di[(1-4C)alkyl]amino, (1-4C)alkanoylamino, (1-4C)alkylthio, (1-4C)alkoxycarbonyl, a (1-3C)alkylenedioxy, an acyl, a carbocyclic or a heterocyclic group, and which may be annulated by a carbocyclic group or by a heterocyclic group, or  
 5 a heterocyclic group,

its stereoisomers, enantiomers and racemates, and salts thereof;

(R<sup>1</sup>)<sub>n</sub> is the same or different halogen atom, a (1-4C)alkyl-, or a (1-4C)alkoxy- group, and n = 0-4.

10 3. A compound of formula ( I ) according to claim 1 or 2, wherein

A is Pyridine, 2-Aminopyridine or Pyrimidine;

B is a substituent, chosen from:

2-Fluoro-6-hydroxy-3-methoxy-phenyl, 2-Fluoro-6-hydroxy-3-methyl-phenyl, 6-Hydroxy-3-methylsulfanyl-phenyl, 6-Hydroxy-2,3-dihydrobenzo[1,4]dioxine-5-yl, 6-Hydroxy-2,3-dimethoxy-phenyl, 2-Hydroxy-5-methoxy-phenyl, 2-Hydroxy-5-methyl-phenyl, 5-Hydroxy-2-methylpyridine-4-yl, 3-Fluoro-5-hydroxy-2-methyl-pyridine-4-yl, 8-Fluoro-6-hydroxy-quinoline-7-yl, 8-Fluoro-6-hydroxy-2-methyl-quinoline-7-yl, 2-tert-Butyl-8-fluoro-6-hydroxy-quinoline-7-yl, 6-Hydroxy-quinoline-5-yl, 3-Dimethylamino-2-fluoro-6-hydroxy-phenyl, 5-Dimethylamino-2-hydroxy-phenyl, 2-Hydroxy-5-piperidin-1-yl-phenyl, 2-Fluoro-6-hydroxy-3-piperidin-1-yl-phenyl, 3-(3,3-Dimethyl-piperidin-2-yl)-2-fluoro-6-hydroxy-phenyl, 3-(3,3-Dimethyl-piperidin-2-yl)-6-hydroxy-phenyl;

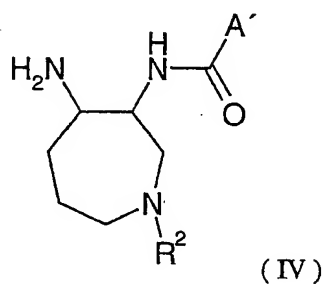
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and n = 0 for ( R<sup>1</sup> )<sub>n</sub>

4. The compound of formula ( I ) according to one of the claims 1, 2 or 3 wherein said compound is an optical isomer of the compound of formula  
 30 ( I ).

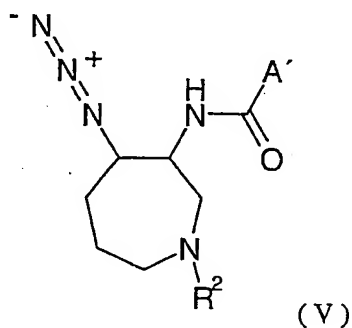
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A compound of formula ( IV ) or the salt thereof



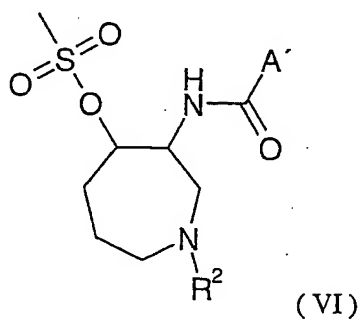
5        wherein A' is a carbocyclic or heterocyclic group, or a suitably protected derivative thereof and R² is a protecting group.

6.    A compound of formula ( V ) or the salt thereof



wherein the remaining symbols have the significance given in claim 5.

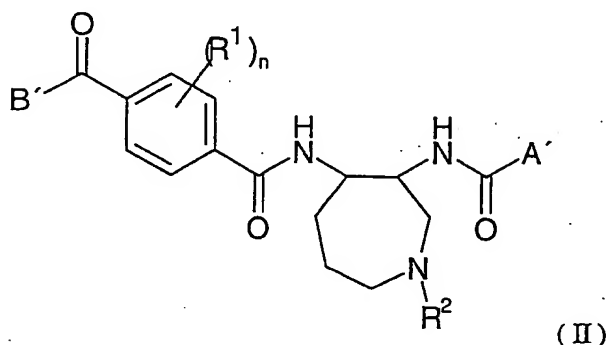
10    7.    A compound of formula ( VI ) or the salt thereof



wherein the remaining symbols have the significance given in claim 5.

A compound according to any of the claims 5 to 7, wherein said compound is an optical isomer of any of the compounds according to claims 5 to 7.

9. A process for the manufacture of the compounds as claimed in one of claims 1 to 3, characterized by cleaving off the protecting group  $R^2$  and, if necessary, protecting groups present in  $A'$  and  $B'$  from a compound of the formula



10. wherein  $B'$  represents  $B$  as defined in claim 1, 2 or 3 or a protected derivative thereof,  $R^1$  has the significance given in claim 1, 2 or 3, and the remaining symbols have the significance given in claim 5,

if necessary, converting the obtained compound of formula (I) into a salt.

10. A process according to claim 9, wherein compounds of the formula (II) are obtained by using compounds of formulas (IV), (V) and (VI) as intermediates.
11. A composition containing a compound of formula (I) or a salt thereof as claimed in one of claims 1 to 4 and usual adjuvants.
12. A pharmaceutical composition, containing a compound of formula (I) or a salt thereof as claimed in one of claims 1 to 4 as the active ingredient and usual pharmaceutical adjuvants.



The use of a compound of formula ( I ) or a salt thereof as claimed in one of claims 1 to 4 for the production of medicaments for the therapy and prophylaxis of illnesses which are mediated by protein kinases.

- 5           14. The use of a compound of formula ( I ) or a salt thereof as claimed in one of claims 1 to 4 for the production of medicaments for the therapy and prophylaxis of cancer.
- 10          15. A method for the treatment of cancer in a patient in need of such treatment, comprising administering to the patient an amount of a compound of formula ( I ) or a salt thereof as claimed in one of the claims 1 to 4, wherein the amount is effective for such treatment.